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BAH

US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Dockets Management Branch (HFA-305)
[docket no. 00D-1392]
5630 Fishers Lane
Room 1061
Rockville, MD 20852
USA

October 7, 2000

FDA Draft Guidance for Industry on Botanical Drug Products, August 2000

Dear Sirs:

Please find attached several comments of BAH, the German Self-Medication Manufacturers' Association, on the above mentioned document.

Sincerely

Barbara Steinhoff

Dr. Barbara Steinhoff

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BUNDESFACHVERBAND DER
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BAH

**Comments of
Bundesfachverband der Arzneimittel-Hersteller e. V. (BAH),
the German Medicines Manufacturers Association, on
FDA Draft Guidance for Industry on Botanical Drug Products,
issued by U.S. Department of Health and Human Services,
Food and Drug Administration,
Center for Drug Evaluation and Research (CDER),
August 2000**

BAH represents about 300 companies marketing medicinal products mainly in the field of self-medication. Among these medicinal products there is a large part of products of herbal origin which are authorized as herbal medicinal products. From the regulatory point of view herbal medicinal products are fully regarded as medicinal products under the German Medicines Law. Before gaining access to the market, approval by the Federal Institute of Drugs and Medical Devices (BfArM) is required; application for pre-marketing approval consists of adequate proof of quality, safety and efficacy. According to the European Directives, the requirements for the proof of safety and efficacy can be fulfilled by a bibliographic application in case of substances or preparations with a well-established medicinal use. Herbal medicinal products have a market share of almost 30 % of the German market of non-prescription bound medicinal products.

BAH in principle appreciates the new guidance document on botanical drug products issued by FDA. It is important that experience gained with products already marketed as dietary supplements is taken into consideration, as well as marketing experience from foreign countries. We are however of the opinion that in some respect it has not been made sufficiently clear in this document how documented foreign marketing experience can be utilized in order to reduce the amount of pharmacological/toxicological and clinical data to be submitted. In detail, our comments are listed as follows:

1. IND Information for Different Categories of Botanicals (VI.A)

According to information provided in the second paragraph, for botanical products previously not being marketed in the United States certain additional information on safety should be provided. In this respect we regard it as useful to include a statement that foreign marketing experience can be taken into consideration. This would imply that, as stated in the next paragraph of the draft, additional information should only be submitted if the product has not been marketed anywhere.

2. Basic Format for INDs (VI.B)

The section on the protocol (5.) states that in general clinical evaluation of botanical drug products for safety and effectiveness "does not differ significantly from evaluation of synthetic or highly purified drugs". From our point of view, this statement is much too strong and does not take well-known substances into consideration for which e.g. non-interventional trials (the so-called "Anwendungs-

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beobachtungen" according to section 67 para 6 of the German Medicines Law) are available. we therefore suggest that such data should be taken into account.

Point 7 of the basic format for INDs contains requirements for content and format for pharmacological and toxicological information. We appreciate in principle that traditional herbal medicines or currently marketed botanical products may require less preclinical information. We also agree that a product which is not currently lawfully marketed in the United States (but elsewhere) may have sufficient information to support clinical studies without standard preclinical testing. For this reason we propose to include a statement that in this respect foreign marketing experience (outside the United States) should be taken into consideration.

Furthermore it is stated in this paragraph that "after initial clinical studies, further pharmacology and toxicology studies of a botanical drug would generally be needed prior to later phases of clinical developments and prior to approval for marketing". In this respect, we would like to suggest to take into consideration that in case of existing foreign marketing experience, e.g. when a marketing authorization has been granted in a Member State of the European Union according to the European Directives, further pharmacological and toxicological studies should not be required. Reference is made to a proposal "Non-clinical testing of herbal drug preparations with long-term marketing experience" prepared by the Working Group on Herbal Medicinal Products of the European Agency for the Evaluation of Medicines (EMEA). This guidance states that where there is sufficient experience available in humans, several tests such as single-dose and repeated-dose toxicity, immunotoxicity, local tolerance testing etc. are not required. The expert report however must address these aspects and give the grounds why the documented medical experience justifies a safe use of the product.

3. INDs for Phase 1 and Phase 2 clinical studies of lawfully marketed botanical products (VII.)

• Description of the product (VII.A.3)

In this paragraph information about the nature and the extent of the current worldwide use is required. We appreciate that in this respect market data from foreign countries outside the United States can be taken into consideration. We are however wondering which are the consequences on the requirements for pharmacological and toxicological testing.

• Chemistry, Manufacturing and Control (VII.B.3)

This paragraph demonstrates how the active component of the product should be declared, e.g., Senna leaf extract (1:8 powdered aqueous extract) 250 mg.

From our point of view, Senna leaf extract is not a good example for this kind of declaration. Senna belongs to the very few cases of medicinal plants where constituents with known therapeutic activity are known, in this case hydroxyanthraquinone derivates (which are calculated as sennoside B according to the European Pharmacopoeia).

For this reason we would like to propose that in case constituents with known therapeutic activity are known, e.g. Senna, the herbal drug preparation should be standardized to a certain amount of these substances. This is in accordance with the European Guideline "Quality of Herbal Remedies" (November 1988) as revised by the EMEA Working Group on Herbal Medicinal Products in 1998.

• Labelling (VII.B.5)

Furthermore, for the labelling a statement "Caution: New Drug" is required. From our point of view, this statement is not considered appropriate because in case of lawfully marketed herbal products, the herbal preparation is already well-known and accepted by the consumers.

• Pharmacology/Toxicology Information (VII.C)

Concerning pharmacology/toxicology information of foreign-marketed botanical products the sponsor should "provide data that the support safe human use...". From our point of view, there should no further pharmacological/toxicological data be required if the product is already authorized as a drug in a Member State of the European Union, i.e. safety has been proven by appropriate means according to the European Directives on marketing authorization.

• Bioavailability (VII.D)

In terms of bioavailability, the blood levels of known active ingredients should be monitored. As stated above, in most cases constituents with known therapeutic activity are not known (except very few cases). For this reason blood levels cannot be determined. It is not useful to determine marker substances which have nothing to do with a therapeutic activity but only represent analytical means.

• Clinical Considerations (VII.E)

Regarding clinical considerations we do not support the statement that uncontrolled observations are unlikely to be useful. As stated above, non-interventional trials (e.g. the so-called "Anwendungsbeobachtungen" according to section 67 para 6 of the German Medicines Law) can be used to support safety and efficacy.

4. INDs for Phase 1 and Phase 2 Clinical Studies of Nonmarketed Botanical Products (VIII.)

In terms of bioavailability, the same applies as stated under 3. for legally marketed products.

5. INDs for Phase 3 Clinical Studies of All Botanical Products (IX.)

• Preclinical Safety Assessment (IX.C)

It is stated that "a botanical product submitted for approval for marketing as a drug will be treated like any other new drug under development. Previous human experience may be insufficient to demonstrate safety of a botanical product, especially when it is indicated for chronic therapy." From our point of view this

statement is not adequate for products already marketed. We therefore strongly recommend to differentiate between marketed products and non-marketed products within this chapter. Such a differentiation, whether marketing experience already exists or not, is in accordance with the above mentioned guidance "Non-clinical testing of herbal drug preparations with long-term marketing experience" of the EMEA (1998). Furthermore we recommend to include a statement that foreign marketing experience outside the United States should be taken into consideration.

• Clinical considerations (IX.E)

The same applies for clinical considerations (chapter E), in particular for the statement that "expanded studies of botanical products have the same purposes as expanded studies of synthetic drugs, including further evaluation of dose-response for favorable and unfavorable effects and evaluation of long-term effectiveness, different populations, different stages/severity of disease and drug-drug interactions." We are of the opinion that also in case of clinical considerations the established use of a product e.g. as a dietary supplement as well as foreign marketing experience e.g. from Member States of the European Union have to be taken into consideration resulting in reduced requirements for the submission of data.

October 5, 2000/St/la

Note for Guidance "Quality of Herbal *Medicinal Products*" (July 1998)

Note for Guidance concerning the application of Part *2* of the Annex to Directive 75/318/EEC, as amended. The special problems of herbal ***medicinal products*** and the differences between medicinal products containing chemically defined active ***substances*** are described in this Note for Guidance(*).

This Note for Guidance should be read in conjunction with the Annex 7 "Manufacture of Herbal Medicinal Products" of Good Manufacturing Practice (GMP) for medicinal products; GMP recommendations should be respected.

Consistent quality for products of ***herbal*** origin can only be assured if the starting materials are defined in a rigorous and detailed manner including especially the specific botanical identification of the plant material used. It is also important to know the geographical source and the conditions under which the ***herbal*** drug is obtained to ensure material of consistent quality.

Reference substances used in the control of all stages of the manufacturing process should be *specified*.

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE *ACTIVE SUBSTANCE(S) OF A HERBAL MEDICINAL PRODUCT*

1) In the case of a ***herbal*** drug ***or of a herbal drug preparation consisting of reduced, comminuted or powdered herbal drugs***

either (i) the ***native*** quantity of a ***herbal*** drug ***or of a herbal drug preparation shall*** be stated ***if constituents with known therapeutic activity are unknown***

or (ii) the ***native*** quantity of a ***herbal*** drug ***or of a herbal drug preparation shall*** be given as a range corresponding to a defined quantity of constituents with known therapeutic activity.

EXAMPLE

i) Active *substance*

Name	Quantity (**)
Valerianae radix	900 mg

Other substance(s)
Name
...

ii) Active *substance*

Name	Quantity
Sennae folium	415-500 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as Sennoside B.

Other *substance(s)*
Name
...

(*) In this Note for Guidance, the sequence used is designed to relate directly to Part *2* of the Annex to Directive 75/318/EEC, as amended.

(**) ***The quantity indicated refers to the specifications provided in the documentation.***

2) In the case of a *herbal* drug preparation ***produced by steps which exceed comminution and reduction, the nature and concentration of the solvent and the physical state of the extract have to be given. Furthermore the following has to be indicated:***

either (i) the equivalent quantity ***x - y*** [*], or the ratio ***a - b: 1***[*] of the ***herbal*** drug to the ***herbal*** drug preparation ***shall*** be stated ***if constituents with known therapeutic activity are unknown*** (this does not apply to fatty or essential oils).

or (ii) ***if the constituents with known therapeutic activity are known***, the quantity of the *herbal* drug preparation may be given as a range corresponding to a defined quantity of *these* constituents (see example).

The composition of any solvent or solvent mixture and the physical state of the extract must be indicated.

If any other substance is added during the manufacture of the ***herbal*** drug preparation to adjust the *herbal* drug preparation to a ***defined content*** of constituents with known therapeutic activity, or for any other purpose, the added substance must be mentioned as an "other ***substance***" and the genuine extract as the "active ***substance***".

EXAMPLE

i) Active *substance*

Name	Quantity
Valerianae radix dry extract ethanolic 60% *(V/V)* *(a - b : 1)*	125 mg
or	
Valerianae radix dry extract ethanolic 60% *(V/V)*	125 mg *equivalent to x - y mg Valeriane radix*

Other substance(s)
Name
...

or

ii) Active *substance*

Name	Quantity
Sennae folium dry extract ethanolic 60% *(V/V)* *(a - b: 1)*	50-65 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as Sennoside B

Other *substance(s)*
Name
...

B. DESCRIPTION OF THE METHOD OF PREPARATION

The manufacturing process within the meaning of this section is the preparation of the finished product from *herbal drug(s) or herbal drug preparation(s)*. The description should include details of *the process together with the controls exercised. This section should be in accordance with the "Note for Guidance on Manufacture of the finished dosage form" (CPMP/QWP/486/95).* If *herbal*

[*] *'a' and 'b' or 'x' and 'y' have to be justified by the applicant*

drug preparations are the starting material, the manufacture of the *herbal* drug preparations and their controls do not belong under this section but under section C.

C. CONTROL OF STARTING MATERIALS

1) Control of the *herbal* drug *and of herbal drug preparations*

- *Control of the herbal drug*

A ***comprehensive specification*** for each ***herbal*** drug must be submitted, even if the starting material is a ***herbal*** drug preparation. This also applies if the applicant is not the manufacturer of the preparation. In the case of fatty or essential oils ***used as active substances of herbal medicinal products,*** a ***specification*** for the ***herbal*** drug is ***required unless fully justified.*** The scientific name of the parent plant and its part(s) have to be stated.

If no monograph for the ***herbal*** drug is given in a Pharmacopoeia referred to in Directive 75/318/EEC, Annex 1, a ***comprehensive specification*** on the ***herbal*** drug must be supplied and should be set out in the same way where practicable, as the monographs on ***herbal*** drugs in the European Pharmacopoeia. This should include the botanical name and authority and the common name if used for labelling purposes. Information on the site of collection, the time of harvesting and stage of growth, treatment during growth with pesticides etc., and drying and storage conditions should be included if possible. The ***comprehensive specification*** should be established on the basis of recent scientific data. In the case of ***herbal*** drugs with constituents of known therapeutic activity, assays of their content (with test procedure) are required. The content must be included as a range, so as to ensure reproducibility of the quality of the finished product. ***In the case of herbal drugs where constituents of known therapeutic activity are not known, assays of marker substances (with test procedure) are required. The choice of markers should be justified.***

As a general rule, ***herbal*** drugs must be tested for microbiological quality and for residues of pesticides and fumigation agents, toxic metals, likely contaminants and adulterants, etc., unless otherwise justified. ***Radioactivity should be tested if there are reasons for concerns.*** Specifications and descriptions of the analytical procedures must be submitted, together with the limits applied. ***Analytical procedures not given in a Pharmacopoeia should be validated in accordance with the ICH guideline "Validation of analytical procedures: methodology" (CPMP/ICH/281/95).***

Reference samples of the ***herbal*** drugs must be available for use in comparative tests e.g. macro and microscopic examination, chromatography etc.

- *Control of herbal drug preparations*

If the herbal ***medicinal product*** contains not the ***herbal*** drug itself but a preparation, the ***comprehensive specification*** on the ***herbal*** drug must be followed by a description and validation of the manufacturing process for the ***herbal*** drug preparation. ***The information may be supplied either as part of the marketing authorisation application or using the European Drug Master File procedure. If the latter is chosen the documentation should be submitted in accordance with the Note for Guidance "European Drug Master File Procedure for Active Substances" (Eudra/Q/93/014).***

For each ***herbal*** drug preparation, a ***comprehensive specification*** must be submitted. This must be established on the basis of recent scientific data and must give particulars of the characteristics, identification tests and purity tests. This has to be done e.g. by different appropriate chromatographic methods. If deemed necessary by the results of the analysis of the starting material, tests on microbiological quality, residues of pesticides, fumigation agents, solvents and toxic metals have to be carried out. ***Radioactivity should be tested if there are reasons for concerns.*** Quantitative determination (assay) of ***markers or of substances with known therapeutic activity*** is required. The content must be indicated with the lowest possible tolerance. The test methods must be described in detail.

If preparations from *herbal* drugs with constituents of known therapeutic activity are standardised (i.e. adjusted to a *defined content* of constituents with known therapeutic activity) it must be stated how such standardisation is achieved. If another *substance* is used for this purpose, it is necessary to specify as a range the quantity that can be added.

2) Control of excipients

Excipients including those added during the manufacture of the herbal drug preparations should be described according to the "Note for Guidance on Excipients in the dossier for application for marketing authorisation of a medicinal product" (Eudra/Q/91/015).

D. CONTROL TESTS CARRIED OUT AT AN INTERMEDIATE STAGE OF THE MANUFACTURING PROCESS OF THE FINISHED PRODUCT

Details of all control tests with details of test procedures and limits applied at any intermediate stages of the manufacturing processes are required, especially if these tests cannot be done in the finished product.

E. CONTROL TESTS ON THE FINISHED PRODUCT

This section should be in accordance with the "Note for Guidance on Specifications and control tests on the finished product" (Eudra/Q/91/020) and the analytical procedures should be validated according to the ICH guideline "Validation of analytical procedures: methodology" (CPMP/ICH/281/95).

The control tests on the finished product must be such as to allow the qualitative and quantitative determination of the composition of the active *substances* and a specification has to be given which may be done by using markers if constituents with known therapeutic activity are unknown. In the case of *herbal* drugs or *herbal* drug preparations with constituents of known therapeutic activity, these constituents must also be specified and quantitatively determined.

If a herbal *medicinal product* contains several *herbal* drugs or preparations of several *herbal* drugs and if it is not possible to perform a quantitative determination of each active *substance*, the determination may be carried out jointly for several active *substances*. The need for this procedure must be justified.

The criteria given by the European Pharmacopoeia to ensure the microbiological quality should be applied unless justified.

F. STABILITY TESTS

This section should be in accordance with the "Note for Guidance on Stability testing of new active substances and medicinal products" (Eudra/Q/92/021) and the "Note for Guidance on stability testing of existing active substances and related finished products" (CPMP/QWP/556/96).
Since the *herbal* drug or *herbal* drug preparation in its entirety is regarded as the active *substance*, a mere determination of the stability of the constituents with known therapeutic activity will not suffice. It must also be shown, as far as possible e.g. by means of appropriate fingerprint chromatograms, that other substances present in the *herbal* drug or in the *herbal* drug preparation are likewise stable and that their proportional content remains constant.

If a herbal *medicinal product* contains several *herbal* drugs or preparations of several *herbal* drugs and if it is not possible to determine the stability of each active *substance*, the stability of the medicinal product should be determined by appropriate fingerprint chromatograms, appropriate

overall methods of assay and physical and sensory tests or other appropriate tests. *The appropriateness of the tests shall be justified by the applicant.*

In the case of herbal drug preparations containing constituents with known therapeutic activity, the limit should be ± 5% of the initial assay value unless justified. In the case of constituents without known therapeutic activity, a limit of ±10% of the initial assay value can be accepted if justified by the applicant. These criteria shall apply to the stability testing of active substances in like manner.

ANNEX

GLOSSARY

Herbal *medicinal products* are medicinal products containing as active ***substances*** exclusively ***herbal drugs*** or ***herbal*** drug preparations.

Herbal drugs are ***plants***(*) ***or part of plants in an unprocessed state, which are*** used for a medicinal ***or pharmaceutical*** purpose. A ***herbal*** drug or a preparation thereof is regarded as one active ***substance*** in its entirety whether or not the constituents with therapeutic activity are known.

Herbal drug preparations are comminuted or powdered ***herbal*** drugs, extracts, tinctures, fatty or essential oils, expressed juices, ***processed resins or gums***, etc...prepared from ***herbal*** drugs, and preparations whose production involves a fractionation, purification or concentration process. However, chemically defined isolated constituents or their mixture are not ***herbal*** drug preparations. Other ***components*** such as solvents, diluents, preservatives may form part of ***herbal*** drug preparations. These ***components*** must be ***declared***.

Constituents with known therapeutic activity are chemically defined substances or groups of substances which are ***generally accepted*** to contribute ***substantially*** to the therapeutic activity of a ***herbal*** drug or of a preparation.

Markers are chemically defined constituents of a ***herbal*** drug which are of interest for control purposes ***independent of whether they have any therapeutic activity or not***. Markers may serve to calculate the quantity of ***herbal*** drug or preparation in the finished product if that marker has been quantitatively determined in the ***herbal*** drug or preparation when the starting materials were tested.

Standardisation(**) ***means adjusting the herbal drug preparation to a defined content of a constituent or a group of substances with known therapeutic activity respectively by adding excipients or by mixing herbal drugs or herbal drug preparations (e.g. standardised extract from the European Pharmacopoeia).***

(*) *Thallophytes, especially lichens, higher fungi and algae, are included in like manner*

(**) *In some Member States the expression "standardisation" is used on a national level to describe all measures which are taken during the manufacturing process and quality control leading to a reproducible quality*

PROPOSAL FOR NEW GUIDANCE

"Non-clinical testing of herbal drug preparations with long-term marketing experience"
Guidance to facilitate mutual recognition and use of bibliographic data

INTRODUCTION

Article 4 point 8 a) ii) of Council Directive 65/65/EEC makes it clear that the applicant shall not be required to provide the results of pharmacological and toxicological tests if he can demonstrate by detailed reference to published scientific literature presented in accordance with the second paragraph of Article 1 of Council Directive 75/318/EEC that the constituent(s) of the medicinal product have a well-established medicinal use, with recognised efficacy and an acceptable level of safety. This regulation in no way relaxes the requirements of proof of safety set out by the Annex to Council Directive 75/318/EEC. All aspects must be covered by appropriate bibliographic data and the expert report.

Published non-clinical tests for well-established herbal drug preparations are often incomplete or not in accordance with today's state of the art. Well-presented clinical experience (with regard to the time and extent of use in humans) as well as post-marketing experience gained by wide spread use in humans contribute to the avoidance of unnecessary tests in animals. Protection of animals should be taken into consideration when requesting non-clinical testing of well-established herbal drug preparations (86/609/EEC). Studies that do not agree with the current state of the art (e.g. GLP-conformity), should be judged for credibility; subsequent demands that could lead to a "blind" repetition of animal experiments should be avoided. In particular, it should be assessed whether the observed effects in animals studies would modify the benefit/risk assessment and would lead to a negative decision for the granting of a Marketing Authorisation.

In cases of reasonable suspicion, additional appropriate non-clinical tests can be requested.

NON-CLINICAL TESTING

Where there is sufficient experience available in humans, single dose and repeated dose toxicity, immunotoxicity as well as local tolerance testing of well-established herbal drug preparations is not necessary. Likewise, pharmacological tests including safety pharmacology and pharmacokinetics are not necessary. The expert report must address these aspects and give the grounds why the documented medical experience justifies a safe use of the herbal drug preparation.

Non-clinical testing of well-established herbal drug preparations should be directed towards the study of effects that are difficult, even impossible to detect clinically. These effects would include toxicity to reproduction, genotoxicity and carcinogenicity.

Reproductive toxicological investigations regarding fertility are generally not necessary, insofar as there are no grounds for suspicion that would necessitate testing.

The reproductive toxicological potential with regard to embryo-foetal and peri-post-natal development is to be clarified. Reproductive toxicity data are available for many old substances, however, these data are often not reliable. A repetition of the tests is only justified in cases in which the significance of the results is not clear and there are grounds for suspicion. Reproductive toxicological tests in animals are not necessary if one of the following criteria is fulfilled:

- Results from epidemiological data of adequate power or post-marketing safety studies are available.
- Results from investigations in pregnant women and neonates are present.
- The medicinal product is not intended to be used in women of child-bearing age or during pregnancy and lactation.

The clinical Expert Report should justify the distinction made between women of child-bearing age and pregnancy.

The genotoxic potential of herbal drug preparations should be clarified.

A repetition of the studies is only required in cases in which the significance of the results is unclear or they yield grounds for suspicion. Positive findings for one herbal drug preparation or for substances from one chemical class can frequently be extrapolated to another herbal drug preparation without necessitating further testing.

It is recommended to first perform *in vitro* tests for substances in which the genotoxicity tests are insufficient. Substances with negative results *in vitro* also exhibit negative results *in vivo* in the majority of cases. In cases in which positive results in vitro are present, these are to be clarified by way of appropriate investigations, mainly *in vivo*. (CPMP Note for Guidance on genotoxicity: a standard battery for genotoxicity testing of pharmaceuticals (CPMP/ICH/174/95), CPMP Note for Guidance on genotoxicity: guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals (CPMP/ICH/141/95) and OECD 1995).

It is appropriate to assess genotoxicity initially in a bacterial reverse mutation test using a test battery of different bacterial strains and metabolic activation (s. CPMP/ICH and OECD Guidelines). This test has been shown to detect relevant genetic changes and the majority of genotoxic rodent carcinogens. If positive results can not be clearly attributed to specific constituents with a well-established safety-profile (e.g. Quercetin) additional *in vitro* and, if necessary, *in vivo* studies should be performed. A co-operative approach is encouraged to investigate herbal drug preparations with the same specification.

Carcinogenicity studies are not needed in cases where there is no suspicion for a carcinogenic potential (Council Directive 75/318/EEC of 20 May 1975, Part 3, IIE. Carcinogenic Potential; CPMP Note for Guidance on the need for carcinogenicity studies of pharmaceuticals (CPMP/ICH/140/95), CPMP Note for Guidance on carcinogenicity: testing for carcinogenicity of pharmaceuticals (CPMP/ICH/299/95), Addendum to Note for Guidance on dose selection for carcinogenicity studies of pharmaceuticals: addition of a limit dose and related notes (CPMP/ICH/366/96)).

Even a positive suspicion of a carcinogenic effect of an well-established herbal drug preparation does not necessarily require a study to be performed. The following considerations should be included in the assessment:

- Is the suspicion based on positive results of genotoxicity studies and can it be clarified in further genotoxicity studies, mainly *in vivo?*
- Is there sufficient epidemiological experience in humans that could refute the suspicion?

EXPERT REPORT

The expert is obliged to point out the necessity or not of non-clinical testing for the herbal drug preparation. Plausible presentation of the facts contributes to the acceptance of the application for marketing authorisation and facilitates the evaluation performed by the authorities.
The expert should discuss available published toxicological data on closely related herbal drug preparations, different parts of the plant, data on related species of the same genus or plant family. If there are toxicological data on well-defined constituents of a herbal drugs preparation, the expert should discuss the relevance of these data f the safety-assessment of the herbal drug preparation.

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